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PERSPECTIVES IN CLINICAL NEPHROLOGY

Chemokines and renal disease

What determines the type of cellular infiltrate in tissue injury?

During the last 100 years pathologists have noted that etiologically different and specific types of inflammatory reactions are associated with infiltration by specific subsets of inflammatory cells. Recent experimental and clinical observations in various forms of kidney diseases have highlighted the importance of interactions of specific leukocyte populations such as neutrophils, monocytes/macrophages and T cells with local renal cells in the disease process (for this review leukocytes are defined as any type of white blood cell) [1]. These studies also demonstrate how the recruitment of specific inflammatory cells to sites of renal injury contributes to both the acute and chronic phase of the specific disease. Conditions that determine the type of cellular infiltrate at the site of injury include: (1.) the local production and release of chemotactic factors; and (2.) activation of inflammatory cells, endothelium and surrounding cells resulting in the expression of adhesion molecules such as selectins and integrins on both the infiltrating inflammatory cells and the local cells.

Previously, several general chemotactic factors have been identified. These included the complement split product C5a, the formyl methionyl peptides (fMLP), leukotriene B4 and platelet activating factor (PAF). While these factors play a substantial role in inflammatory reactions they lack a leukocyte cell-type specificity. The enigma of leukocyte subtype specificity was resolved by the discovery of the superfamily of *chemo*tactic cyto*kines*, named chemokines, where each chemokine exhibits a rather restricted and selective pattern of leukocyte attraction [2, 3]. It is important to stress that chemokines are generated and released locally and are destined for local action. Chemokines appear not to be designed to function systemically, as their systemic administration or general overexpression in transgenic mice will not always lead to the expected phenotypic effects [4].

Thus far, numerous experimental studies and tissue evaluation of patients with a variety of inflammatory diseases of various organs including the kidney support an important role for chemokines in the specific type of leukocyte infiltration [3, 5].

The recent suggestion that chemokines may contribute to slow progression of the HIV infection and the very recent identification of chemokine receptors as docking molecules for HIV infection obviously add tremendous excitement and significance to chemokine research [6–8].

The chemokine family

Chemokines represent a large family of structurally related chemotactic cytokines produced by a variety of immune and nonimmune cells [2, 3]. They are secreted proteins of 8 to 10 kDa molecular weight selectively targeting different leukocyte subpopulations. The complexity of this family is extensive as over 20 distinct human chemokines have been identified to date (Table 1). The chemokine superfamily was originally divided into the C-C and the C-X-C subfamily, which both contain four conserved cysteine residues. In C-C chemokines the first two cysteines are located adjacent to each other, whereas in the C-X-C family, an additional amino acid is interspersed between them. Most C-X-C chemokines are chemoattractants for neutrophils and have no effect on monocytes, whereas C-C chemokines appear to attract mainly monocytes, T cells, natural killer cells, and some granulocytes but no neutrophils. Within the C-X-C family, the majority of the proteins contain at the amino terminal region the amino acid motif E-L-R-C-X-C (glutamic acid-leucine-arginine-cysteine-X-cysteine). Most of these E-L-R-C-X-C chemokines are neutrophil chemoattractants. In contrast, the three C-X-C proteins IP-10, PF4 and Mig, which lack the E-L-R motif, show a different chemotactic spectrum of activities and do bind to different receptor(s). However, after insertion of the E-L-R motif at the amino terminus, PF4 becomes a neutrophil chemoattractant [9]. In this regard, the C-X-C chemokine family is thought to have at least two branches [10]. Recently, a new chemokine has been isolated that belongs neither to the C-C nor the C-X-C subfamily. This protein was named lymphotactin and it represents the first and as yet only member of a new third subfamily called the C chemokines [11]. Lymphotactin lacks two of the four conserved C residues and functions as a potent chemoattractant for T lymphocytes, but does not attract monocytes or neutrophils.

General chemokine function

To understand the biological significance of the chemokines, one must view them in the broader context of leukocyte-endothelial-cellular matrix interactions [12]. The migration of leukocytes from the peripheral circulation into interstitial spaces involves a series of complex interactions between molecules expressed on the leukocyte, the endothelial surface and the extracellular matrix. The process of leukocyte trafficking has been modeled into discrete stages (Fig. 1). The initial stage involves rolling of leukocytes along the microvascular vessel wall through transient interactions between specific selectin proteins and their carbohydrate ligands. The next stage involves activation of the leukocyte resulting in a firm adhesion to the endothelial surface mediated through integrin molecules. The final stage involves extravasation of the leukocyte, which includes crawling along the endothelium, diapedesis, and migration into the interstitial spaces [12].

Chemokines are thought to play a role at pivotal stages in this process: First, chemokines, produced at the site of injury or released by activated platelets, are sequestered in solid phase on the endothelial cell surface (immobilized via electrostatic interactions with negatively charged glucosaminoglycans or presented by distinct structures). Here they act as sign posts for specific types of leukocytes as the circulating cell rolls along the endothelial

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Table 1. The human chemokine superfamily

C-X-C chemokines	
IL-8	Interleukin 8
GROα	Growth-related oncogene alpha
GROβ	Growth-related oncogene beta
GROγ	Growth-related oncogene gamma
ENA-78	Epithelial cell-derived neutrophil-activating protein 78
PF4	Platelet factor 4
IP-10	Interferon-gamma-inducible protein 10
GCP-2	Granulocyte chemotactic protein 2
Mig	Monokine induced by interferon-gamma
SDF-1α	Stromal cell-derived factor 1 alpha
SDF-1β	Stromal cell-derived factor 1 beta
PBP	Platelet basic protein
PBP cleavage products:	
CTAB-III	Connecting tissue activating protein III
β-TG	β-thromboglobulin
NAP-2	Neutrophil activating protein 2
C-C chemokines	
MCP-1	Monocyte chemoattractant protein 1
MCP-2	Monocyte chemoattractant protein 2
MCP-3	Monocyte chemoattractant protein 3
MCP-4	Monocyte chemoattractant protein 4
RANTES	Regulated upon activation, normal T cell expressed and secreted
MIP-1α	Macrophage inflammatory protein 1 alpha
MIP-1β	Macrophage inflammatory protein 1 beta
I-309	—
Eotaxin	—
HCC-1	Hemofiltrate CC chemokine 1
C chemokines	
Ltn	Lymphotactin

surface [12]. These surface bound chemokines can cause activation of leukocytes resulting in the up-regulation of integrins, an arrest of rolling, and firm adhesion of the leukocyte to the endothelial surface. Next, the leukocyte can crawl along a surface bound chemotactic gradient formed by chemokines through a process known as haptotaxis [13, 14] or follow a local solute gradient of chemokines [15]. Finally, at some point the leukocyte extravasates through the endothelium and basement membrane into the tissue space, presumably while still responding to a chemotactic/haptotactic chemokine gradient. In this context it is of special interest that chemokines have also been demonstrated to up-regulate the secretion and activity of matrix metalloproteinases by infiltrating leukocytes [16]. The activation of these enzymes are thought to facilitate leukocyte transmigration through the basement membrane and extracellular matrix [17].

Chemokines can also activate cells that they attract. IL-8 induces neutrophil granule release [18] and the respiratory burst [19]. RANTES will cause basophil and eosinophil degranulation and respiratory burst in eosinophils [20, 21]. In addition, RANTES has been shown to function as a co-stimulatory agent in T cell proliferation [22]. In a broad context, each of these functions can be viewed as part of the inflammatory process in which chemokines appear to play a central role.

Once the specific leukocyte has reached the point of highest chemokine concentration, it will remain there and secrete cytokines and additional chemokines resulting in a local amplification loop and further leukocyte accumulation. At this stage the leukocyte may become the major source of chemokines. The leukocyte accumulation will result in the removal of the initiating insult (such as phagocytosis of bacteria, immune complexes, etc.) and eventual repair of the tissue. The inactivation and removal of the inflammatory cells once their goal has been accomplished is also important, as otherwise a chronic inflammation with progressive tissue destruction and sclerosis will ensue. Factors governing the termination of the inflammatory response could involve ligand mediated down-regulation of chemokine and cytokine synthesis or chemokine receptors by local factors (such as prostaglandins, TGF-β) or a specific combination of inflammatory mediators leading to local apoptosis of the involved leukocytes [23].

Chemokines also display broader biological functions. For example, some chemokines appear to have roles in hematopoiesis [24]. The MGSA/GROα C-X-C chemokine was originally identified as an autocrine growth factor for a human melanoma cell line [25]. IL-8 is a potent angiogenic factor [26]. PF4 has been shown to inhibit tumor growth, probably through anti-angiogenesis properties, and to inhibit megakaryopoiesis [27]. PF4 has also been shown to reverse Con-A induced immune suppression in mice [28]. Finally, PF4 has also demonstrated bactericidal functions [29]. Further study of the general effects of chemokine expression on angiogenesis and issues of tissue remodeling should prove interesting in the future.

Recently it has been shown that RANTES, MIP-1α and MIP-1β produced by $CD8^+$ T cells dramatically inhibit the replication of HIV *in vitro*. It has been speculated that the production of these chemokines by $CD8^+$ T cells is at least in part responsible for the phenomenon of the "slow progressor" phenotypes seen in some HIV infected individuals [30]. This hypothesis is further supported by the very recent identification of chemokine receptors as necessary cofactors for HIV infection of leukocytes [6–8].

Chemokine genes

The genomic organization and chromosomal localization for many of the C-X-C and C-C chemokine genes has been described in recent reviews [2, 3]. All of the C-C genes have been mapped to human chromosome 17 (q11-21) and to a syntenic region of chromosome 11 in the mouse. The C-X-C chemokines likewise are located as a gene cluster on human chromosome 4 (q12-q21) and chromosome 5 in the mouse. The C chemokine lymphotactin has been localized to chromosome 1 in humans as well as in the mouse [11]. The C-C chemokine genes show a three exon, two intron organization. The C-X-C genes with the exception of PF4 and the PBP genes appear to have a four exon, three intron structure. PF4 and the PBP genes show a three exon, two intron configuration as found in the C-C chemokines.

Chemokines can be rapidly up-regulated upon activation of cells. Detailed studies of the transcriptional regulation have been performed for only some of the chemokines, including IL-8, MCP-1 and RANTES. Members of the NF-κB/Rel family, C/EBP family, and the AP-1 family of transcription factors appear to play a prominent role in the regulation of these chemokine genes [31–34]. The 5′-flanking sequences of the C-X-C chemokines GROα, GROβ and GROγ contain binding motifs for NF-κB [2]. Many of the chemokines are also regulated post-transcriptionally and often contain an AUUUA element in their 3′ untranslated region, which is thought to be involved in mRNA destabilization [35, 36].

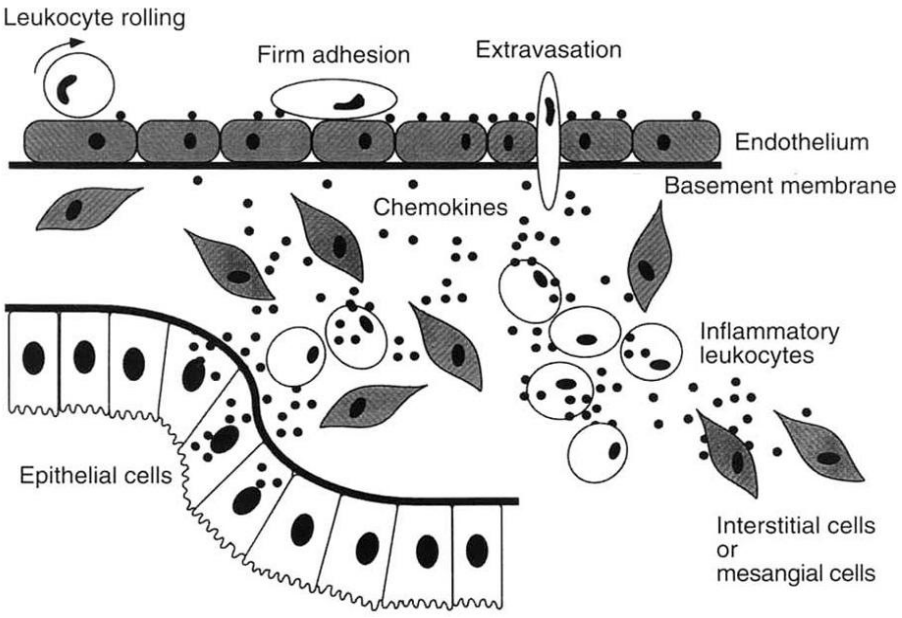

Fig. 1. *Schematic representation of the current model of chemokine involvement in leukocyte trafficking.* For details see text.

Secretion and matrix binding

Chemokine mRNAs contain leader signal sequences that direct the protein to the endoplasmic reticulum and eventually to secretory vesicles. In most cell types, such as endothelial cells, vascular smooth muscle cells, mesangial cells and fibroblasts, chemokines are generated *de novo* and secreted upon stimulation. Platelets, however, can release preformed chemokines upon activation [37].

Most chemokines readily dimerize in solution and undergo oligomerization at high concentrations of protein and at neutral pH. Nevertheless, some chemokines can function as monomers [38, 39]. Chemokines are basic proteins and will bind to heparan sulfate proteoglycans on cell surfaces, or the extracellular matrix, which may be important for the activation and in the haptotactic process as leukocytes migrate from the endothelium and through the interstitium.

Chemokine receptors

The biological effects of the chemokines appear to be mediated through interactions with seven-transmembrane, G-protein coupled receptors [40]. Chemokine concentrations required for receptor binding and cell activation are in the nanomolar range. The chemokine receptor genes are expressed in a cell-type specific manner and this differential expression may be the basis for the specificity of chemokines for subsets of leukocytes. The characterized human chemokine receptors (as of June 1996) are listed in Table 2. During a recent meeting on chemokines, a new nomenclature for the receptors has been agreed upon (Tom Schall, personal communication). In Table 2 the new nomenclature is provided and the previous names are given in parentheses.

Binding of a given chemokine to its receptor(s) leads to activation of phospholipase C $\beta 1$ and $\beta 2$, production of inositol (1,4,5)-trisphosphate and diacylglycerol, a rapid and transient increase in intracellular calcium and the activation of PKC. Many details are still unclear, but it seems that chemokines can activate both G protein dependent and independent signal transduction pathways. Different kinases may be involved in signal transduction, including serine/threonine kinases (such as members of the MAP kinase cascade) as well as tyrosine protein kinases [41].

The known chemokine receptors can be grouped into four different classes, namely the "shared," "specific," "promiscuous" and "virally encoded" receptors [10]. The shared receptors bind

Table 2. Human chemokine receptors

Receptor	Ligand	Expressing cells
CXCR-1 (IL-8RA)	IL-8	N, M, T, NK, Ba
CXCR-2 (IL-8RB)	IL-8 and other E-L-R-C-X-C chemokines	N, M, T, NK
CCR-1 (CC CKR-1)	MIP-1α, RANTES, MCP-3	M, T, NK, B, (N, E)
CCR-2 (CC CKR-2)	MCP-1, MCP-3	M
CCR-3 (CC CKR-3)	eotaxin, RANTES, MCP-3	E, (M, N)
CCR-4 (CC CKR-4)	MIP-1α, RANTES, MCP-1	Ba, M, T, B, P
CCR-5 (CC CKR-5)	MIP-1α, RANTES, MIP-1β	Ma
DARC (=ECKR)	many C-X-C and C-C chemokines	RBC, endothelial cells (kidney), brain

Abbreviations

IL-8RA, IL-8RB	Interleukin 8 receptor type A or B
CXCR-1,2	CXC chemokine receptor (new nomenclature)
CC CKR-1, 2, 3, 4, 5	C-C chemokine receptor (old nomenclature)
CCR-1, 2, 3, 4, 5	CC chemokine receptor (new nomenclature)
DARC	Duffy antigen receptor for chemokines
ECKR	Erythrocyte chemokine receptor
N, E, Ba	Neutrophil, eosinophil, basophil granulocytes
M, T, B	Monocytes, T lymphocytes, B lymphocytes
Ma	Macrophages
NK	Natural killer cells
P	Platelets
RBC	red blood cells

Table 3. Chemokines produced by kidney cells

	MCP-1		RANTES		ENA-78	GROα		GROβ		IL-8	
	+	−	+	−	+	+	−	+	−	+	−
Mesangial cells	TNF-α IL-1β LPS PMA IgG IFN-γ PDGF O_2^-	DMTU TMTU PDTC NAC HMAP cAMP PGE_2 dex genistein herbimycin tyrphostin TPCK	TNF-α IL-1β LPS TNF-β IgG IFN-γ	DMTU TMTU PDTC NAC HMAP cAMP PGE_2 dex		TNF-α IL-1β LPS	genistein	TNF-α IL-1β LPS	genistein	TNF-α IL-1β IL-1α	dex
Epithelial cells	TNF-α IL-1β LPS IFN-γ IL-1α		TNF-α IL-1β IL-1α		IL-1β	TNF-α IL-1β LPS		TNF-α IL-1β LPS		TNF-α IL-1β	
Endothelial cells	TNF-α IL-1β PMA		TNF-α IL-1β							TNF-α IL-1β	
Interstitial cells			TNF-α IL-1β							TNF-α IL-1β	

Symbols are: +, up-regulation; −, inhibition.

more than one chemokine within either the C-X-C or the C-C subfamily. The IL-8 receptor type B (CXCR-2), which binds C-X-C chemokines containing the E-L-R motif as well as the CC chemokine receptors CCR-1 to CCR-5, belong to this class [42, 43]. The "shared" CCR-1 to -5 receptors have recently become a major focus of HIV research as they appear to be co-factors for the infection of $CD4^+$ cells with HIV [44–46]. The "specific" receptors bind only one chemokine. So far the IL-8 receptor type A (CXCR-1) represents the only example of this class [47]. The third type, or promiscuous chemokine receptor, binds both C-X-C and C-C chemokines and it is found on the surface of erythrocytes [48]. This so-called Duffy antigen receptor for chemokines (DARC) is the recognition structure for the malarial parasite *Plasmodium vivax* [49]. DARC is also found on the endothelium of postcapillary venules in many organs including the kidney [50]. It is thought that the erythroid expressed DARC may act as a means of clearing chemokine from the circulation to prevent these agents from acting systemically. The DARC found on postcapillary venules may be involved in presentation of chemokines on the endothelial surface. The fourth type of chemokine receptor has been found to be encoded within viral genomes [45, 51]. The virally encoded chemokine receptors exhibit superior binding and signaling properties relative to the human receptor analogues. The role of these receptors in viral pathogenesis is at present unclear.

Little is known about the effect of chemokines on protein expression in target cells. So far, only adhesion molecules and cytokines have been analyzed. MCP-1 can induce the expression of β-2 integrins and the production of interleukin 1 and interleukin 6 in human monocytes [52]. In another study, MCP-1, MIP-1α and RANTES were shown to increase the expression of the β-2 integrins CD11b/CD18 and CD11c/CD18, but had no effect on CD11a [53].

Expression of C-C chemokines in renal cells

Before reviewing the *in vivo* expression of chemokines in renal tissue and renal disease we will summarize their production by specific renal cells *in vitro* (Table 3). The expression of the MCP-1 gene has been studied intensively in renal tissues and was recently reviewed [54]. MCP-1 can be induced in cultured mesangial, tubular epithelial and endothelial cells. These experiments were performed using primary cell cultures and some transformed cell lines.

In cultured mesangial cells MCP-1 is up-regulated in a dose-dependent manner by stimulation with tumor necrosis factor-alpha (TNF-α) [55], interferon-gamma (IFN-γ) [56, 57], interleukin-1beta (IL-1β) [58], platelet-derived growth factors PDGF-AB and PDGF-BB [59], lipopolysaccharide (LPS) [60], or phorbol myristate acetate (PMA). Co-stimulation with PDGF and IL-1β shows a synergistic effect [59]. MCP-1 expression is also induced by immunoglobulin G (IgG) complexes, an effect mediated through the immunoglobulin-Fc receptor [61]. In general, the up-regulation of MCP-1 occurs rapidly, peaks after two to six hours and returns within 24 hours to baseline. While transcriptional regulation of MCP-1 is important to the up-regulation of this gene, post-transcriptional regulation through alterations in mRNA stability may also occur [62].

In human renal cortical epithelial cells expression of MCP-1 can be up-regulated by IL-1β and IFN-γ and to a lesser extent by TNF-α and LPS. Maximal levels of mRNA were found six hours after stimulation, and MCP-1 protein was detected after 8 to 12 hours [63]. Similarly, human proximal tubular epithelial cells also express MCP-1 following stimulation by IL-1α and TNF-α in a time- and dose-dependent manner [64]. Endothelial cells cultured from bovine glomeruli were found to constitutively express

MCP-1 mRNA. Levels of MCP-1 mRNA could be increased by stimulation with TNF-α, IL-1β or PMA [65].

The chemokine RANTES is expressed by mesangial cells, tubular epithelium and fibroblasts following stimulation with TNF-α, IL-1β, LPS or TNF-β [66]. The induction of RANTES by TNF-α and IL-1β is augmented by co-stimulation with IFN-γ [67]. IgG complexes can also up-regulate RANTES [68]. In rat derived tubular epithelial cells RANTES expression is induced by TNF-α and IL-1α [69]. In mouse mesangial cells RANTES mRNA was detected two hours after stimulation with TNF-α and levels peaked by 24 hours [70].

Expression of C-X-C chemokines in renal cells

IL-8 is produced in mesangial, epithelial and endothelial cells as well as in renal fibroblasts following stimulation with TNF-α and IL-1β (Table 3) [71]. Pretreatment of the mesangial cells with dexamethasone resulted in a reduced induction of IL-8 [72]. Stimulation of human renal cortical epithelial cells with TNF-α, LPS or IL-1β enhanced expression of IL-8, whereas IFN-γ had no effect [63].

The expression of ENA-78 has so far only been demonstrated for human renal tubular epithelial cells. Increased expression was found after stimulation with IL-1β. Surprisingly, neither TNF-α, IFN-γ nor LPS showed any effect [73].

The chemokines CINC and MIP-2, rat homologues of human GROα and GROβ respectively, are produced by mesangial and epithelial cells in response to stimulation with TNF-α, IL-1β and LPS [12]. The cytokine TGF-beta failed to stimulate CINC and MIP-2 expression. In rat mesangial cells the up-regulation of CINC and MIP-2 could be attenuated by the tyrosine kinase inhibitor genistein [74].

Second messengers involved in chemokine gene regulation

The second messengers involved in chemokine expression by renal cells have been studied by several groups. Reactive oxygen species (ROS) have been implicated as second messenger intermediates for TNF-α and IgG induced stimulation. Radical scavengers such as di- and tetramethylthiourea (DMTU and TMTU), pyrrolidone-dithiocarbamate (PDTC) or N-acetyl cysteine (NAC) attenuate TNF-α or IgG induced up-regulation of MCP-1 and RANTES [68, 75]. Generation of superoxide anions by exogenous xanthine oxidase and hypoxanthin increases MCP-1 and RANTES mRNA levels. TNF-α, IL-1β and IgG complexes can activate a membrane-bound NADPH-oxidase resulting in superoxide generation, which may up-regulate MCP-1 expression. Consistent with this hypothesis is the finding that inhibition of the NADPH-dependent oxidase causes attenuation of MCP-1 and RANTES expression in response to stimulation by TNF-α or IgG [68, 75].

An increase in intracellular levels of cAMP will inhibit expression of some cytokines [76]. In mesangials cells the expression of MCP-1 and RANTES is also attenuated by agents known to increase levels of cAMP such as PGE_2, forskolin or phosphodiesterase inhibitors [56].

In bovine glomerular endothelial cells the induction of MCP-1 expression seen with TNF-α or IL-1β could be inhibited by addition of the protein tyrosine kinase (PTK) inhibitor genistein. The protein kinase C (PKC) inhibitors staurosporine and H7 and the protein kinase A (PKA) inhibitor H-89 show no effect. Stimulation with PMA, which acts as an protein kinase C activator, was only suppressed by protein kinase C inhibitors [65]. Similarly, in human mesangial cells the PTK inhibitors genistein, herbimycin A and tyrphostin cause a dose-dependent inhibition of MCP-1 expression in response to IL-1β induction, whereas PKC or PKA inhibitors show no effect [77].

The transcription factor NF-κB appears to play a major role in control of chemokine gene expression. Recently, the activation of NF-κB in mesangial cells has been examined. Stimulation with TNF-α and IgG complexes causes an increase in nuclear NF-κB [78]. The radical scavenger PDTC and the inhibitor of the NADPH-dependent oxidase HMAP attenuated the increase in nuclear NF-κB in response to TNF-α or IgG complexes, suggesting a potential role for ROS in the activation of NF-κB. This is further supported by the observation that generation of superoxide anions by xanthine oxidase and hypoxanthine increased nuclear NF-κB and MCP-1 expression. This effect could be inhibited by increasing intracellular cAMP levels with PGE_2, forskolin or 8 Br-cAMP [56, 78]. These results could be explained by assuming that stimulation of mesangial cells with TNF-α or IgG complexes leads to generation of ROS which enhance chemokine gene expression by activation of NF-κB. The activation of NF-κB and chemokine expression may be down-regulated by raising intracellular cAMP levels which may represent an important feedback loop. Similarly, IL-1 leads to an activation and nuclear translocation of NF-κB that correlated with increased transcription of MCP-1. Activation of NF-κB is prevented by the inhibitory component of NF-κB, that is, IκB. When proteolytic inactivation of IκB is prevented by the protease inhibitor tosyl-phe-chloromethylketone (TPCK) NF-κB cannot be activated, and this also inhibits MCP-1 expression [79]. These results further support a role for NF-κB in chemokine expression. The inhibitory effect of dexamethasone on chemokine expression may also be mediated by interference with NF-κB activation [80]. In other systems dexamethasone has been shown to both increase IκB levels and to decrease NF-κB activity in the nucleus [81]. In the future, therapeutic considerations on inhibitory actions of prostaglandins and glucocorticoids will obviously be of great interest.

Expression of chemokines in animal models of kidney diseases

The investigation of chemokine involvement in renal diseases represents a logical step as different types of leukocytes play major roles in acute and chronic renal injury. So far the C-C chemokines MCP-1, MIP-1α, MIP-1β, and RANTES and the C-X-C chemokines GROα, GROβ, IL-8, IP-10 and PF-4 have been examined in animal models.

The anti-thymocyte antiserum (anti-Thy 1.1) induced model of glomerulonephritis in rat is characterized by a complement-dependent, initial mesangiolysis, followed by a mesangial proliferative glomerulonephritis with an increase of extracellular matrix, and finally a healing phase. MCP-1 expression in glomeruli was found to be markedly up-regulated as early as 30 minutes after induction of the disease. The immunofluorescence staining of MCP-1 protein revealed a predominant mesangial pattern and some staining in the peritubular capillaries. Concomitantly an increase of glomerular monocyte/macrophage infiltration could be seen. Complement depletion largely prevented the glomerular lesions, as well as the expression of MCP-1, and influx of mononuclear cells into the glomeruli. The findings are consistent with complement-mediated injury by Thy 1.1 antiserum resulting in

early increase of MCP-1 expression and infiltration with monocytes/macrophages [82]. Parallel to the *in vitro* experiments with PGE_2 supression of chemokine generation, pretreatment of rats with PGE_2 also decreased glomerular MCP-1 expression and disease activity [83].

The isolated perfused kidney model allows exclusion of circulating leukocytes as a source of chemokines. In this model perfusion with LPS caused MCP-1 expression especially in peritubular capillary endothelial cells [84]. Glomerular MCP-1 expression can also be stimulated in isolated perfused kidneys after induction of anti-Thy 1.1 nephritis, an effect mitigated by an antagonist of platelet-activating factor (PAF). Perfusion of isolated kidneys with PAF alone increased glomerular MCP-1 mRNA levels as determined by RT-PCR. This suggests that PAF may play a mediator role for the initial MCP-1 expression in the anti-Thy 1.1 model of glomerulonephritis [85]. These intriguing observations will need further confirmation and validation *in vivo*.

The role of IL-8 has been examined in a rabbit model of acute immune complex-mediated glomerulonephritis by using chemokine-neutralizing antibodies [71]. In this model, injection of bovine serum albumin (BSA) lead to glomerular immune complex deposition followed by neutrophil infiltration of the glomeruli and proteinuria. In the glomeruli of control rabbits no IL-8 protein was found by immunohistochemical staining whereas glomerular IL-8 expression was seen in diseased glomeruli. Furthermore, in the rabbits with proteinuria, urinary IL-8 levels were increased. Administration of an neutralizing anti-IL-8 antibody decreased neutrophil influx into the affected glomeruli by 40% and surprisingly abrogated proteinuria completely [71].

Several groups have examined the model af anti-glomerular basement membrane antibody induced glomerulonephritis (anti-GBM GN) in the rat and mouse. Glomerular mRNA expression of the C-X-C chemokines, CINC and MIP-2, was increased as early as 30 minutes after induction of the disease. The first increase in the PF4 or IP-10 mRNA level was found after three hours [74, 86, 87]. The maximum expression was observed between three and six hours and was associated with an increased influx of PMN [87]. Administration of specific antibodies to neutralize CINC or MIP-2 reduced PMN influx into the glomeruli by 40% and concomitantly decreased urinary protein excretion. Complement depletion by cobra venom factor, depletion of leukocytes by irradiation or depletion of PMNs by specific antiserum administration almost completely abrogated the expression of CINC and MIP-2 [74]. A possible conclusion might be that in a local amplification loop PMN contribute directly or indirectly (such as via TNF-α production) to further chemokine production.

In time course experiments MIP-1β mRNA could be detected 30 minutes after induction of the anti-GBM disease. After three hours MIP-1α and MCP-3 mRNA levels were increased. MCP-1 mRNA expression peaked between 6 and 25 hours and persisted up to 96 hours [87–89]. RANTES expression was not increased up to 24 hours [87], but was found on day 3 in one study [88]. The expression of C-C chemokines was associated with mononuclear influx into the diseased kidney. Administration of dexamethasone to rats with anti-GBM nephritis lead to a 50% reduction of glomerular PMN influx and the mononuclear infiltration was nearly completely inhibited. Concomitantly, the glomerular mRNA expression for MIP-2 was decreased by 60% and that for MCP-1 by up to 98% [87]. Renal expression of MCP-1 and RANTES mRNA was also observed in a murine model of anti-GBM nephritis in op/op mutant mice, which lack monocyte-colony stimulating factor (CSF-1) and hence are severely macrophage deficient [90]. Therefore, macrophages could not be the source for MCP-1 and RANTES in the mouse kidneys with anti-GBM nephritis. These data provide initial support for a role of chemokines in the leukocyte infiltration in experimental glomerulonephritis (Fig. 2).

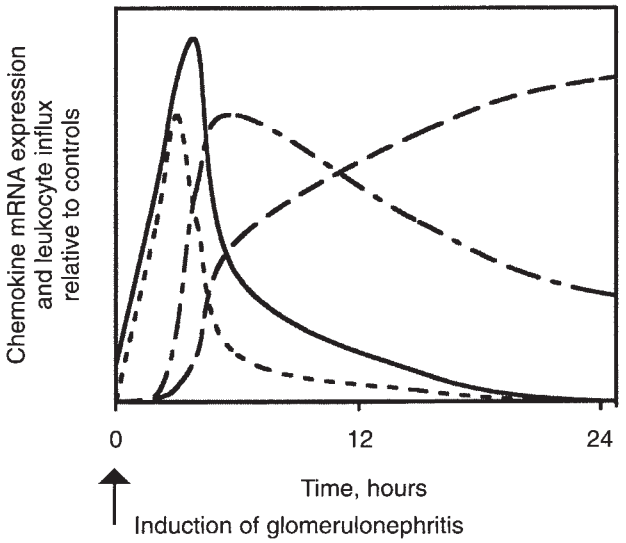

Fig. 2. *Time course of chemokine mRNA levels and leukocyte infiltration in an animal model of anti-GBM antibody-induced glomerulonephritis (based on data from [87, 88]).* Symbols are: (----) MIP-2; (——) PMN; (- - - -) MCP-1; (– – –) monocytes.

Recently Tang, Qi and Warren reported in a preliminary study that pretreatment of rats with a neutralizing anti-MCP-1 antibody before inducing an anti-GBM nephritis resulted in an ~50% decrease in glomerular macrophage infitration and 40% reduction of proteinuria [91]. In contrast, another group could not influence the course of a puromycin-induced nephrotic syndrome in rats by the administration of an anti-MCP-1 antibody [92]. Further investigations will be necessary to determine the role of specific antibodies against chemokines in influencing experimental renal diseases.

In a rat model of anti-tubular basement membrane tubulointerstitial nephritis preliminary RNase protection data suggest an early increase in CINC and MIP-2 expression that is associated with neutrophil infiltration of the kidneys. MCP-1, MIP-1α and MIP-1β were expressed later. These chemokines were localized to the vicinity of infiltrating mononuclear cells in the renal cortex [93].

The expression of chemokines has also been studied in non-immunological disease models. Bilateral renal hilar clamping for 50 minutes served as a rat model for acute ischemic renal failure. KC mRNA, the homologue of GROα, was rapidly detectable, peaked after one hour and decreased to normal levels within 24 hours. JE/MCP-1 mRNA was up-regulated later and persisted 96 hours after inducing ischemia [94]. As ischemic renal failure is also associated with leukocyte infiltration, these results support a role of chemokines in ischemic injury and repair.

In the 2-kidney 1-clip hypertension rat model the "clipped"

kidney represents a model for ischemic lesions, while the nonclipped kidney can be used as a model for hypertensive damage. Differences were found in the expression of chemokines. In the clipped kidney elevated MCP-1 mRNA levels were found at day 2 and during the following 26 days. In the contralateral kidney, an increase in MCP-1 mRNA was seen after 14 days and 28 days and a monocyte/macrophage infiltration was present. The authors suggested that MCP-1 may mediate ischemia and hypertension-induced mononuclear cell infiltration [95].

Unilateral ureteral obstruction in rats as a model of hydronephrosis results in renal cortical macrophage infiltration and later interstitial fibrosis. The expression of MCP-1 mRNA was detected after 12 hours and persisted for four days in the obstructed kidney. Immunohistology revealed increased MCP-1 protein in the cortex. The MCP-1 expression was associated with macrophage influx into the obstructed kidney [96].

The various models of renal diseases support a role for chemokines in leukocyte infiltration. The exact source of the chemokines remains to be determined but could, depending on the models, involve glomerular and tubular epithelial cells, glomerular and peritubular endothelial cells, mesangial and interstitial cells. Furthermore, the possible amplification of chemokine/cytokine expression by infiltrating inflammatory cells, such as PMN may result in a further influx of monocyte/macrophages. The release of chemokines from platelets may explain the detection of chemokine protein by immunohistochemistry in the absence of chemokine mRNA. Future experiments will have to include more detailed immunohistology, *in situ* hybridization, leukocyte and thrombocyte depletion studies, and experiments with genetically modified animals such as transgenic or knockout mice for specific chemokines and their receptors. Thus far, data on MCP-1 transgenic mice [4, 97] and IL-8 receptor homologue knockout mice [98] have been published. The IL-8 receptor homologue knockout mice showed a surprising phenotype. The mice displayed supposed inflammatory responses and migration of neutrophils, but showed in addition a massive overproduction of neutrophils and B cells. Transgenic mice overexpressing MCP-1 in the thymus and the central nervous system were characterized by a higher number of mononuclear cells in these tissues [97].

Chemokine expression in kidney biopsies

Glomerular diseases

Prodjosudjadi and colleagues have examined the expression of MCP-1 by immunohistology in normal human kidneys and in 50 kidney biopsies with various diseases, including transplants [99]. The intensity and the distribution of the fluorescent signal correlated with the local infiltration of macrophages. In control kidneys, a weak staining for MCP-1 was seen in tubular epithelial cells. It is unclear if this represents nonspecific background staining. A significant increase of glomerular staining was found in membranous nephropathy. Surprisingly, strong tubular epithelial staining was found in membranous nephropathy, IgA nephropathy and glomerulosclerosis. It is possible that proximal tubular cell protein and lipid overload secondary to the marked proteinuria causes production of chemokines by tubular cells. In glomerulosclerosis enhanced tubular MCP-1 staining was associated with an increased number of infiltrating macrophages in the interstitium. Surprisingly, MCP-1 expression was not found in transplant rejection although a large number of infiltrating macrophages was present. These authors also found no MCP-1 staining in extracapillary proliferative GN, membranoproliferative GN, lupus nephritis and chronic ischemia although all these diseases are associated with monocyte infiltration [64, 99]. Wada and colleagues [100] performed immunohistochemistry and *in situ* hybridization studies for MCP-1 in biopsies of SLE patients. MCP-1 was detected in peritubular capillaries, in infiltrating monocytes and in cortical tubular cells, but surprisingly not in glomeruli [100]. Different results were obtained in another study [101]. Using immunohistology, positive staining for MCP-1 was found in glomeruli from biopsies of patients with proliferative GN, Wegeners disease and lupus nephritis. The staining pattern was focal and seemed to have a mesangial distribution. Negative staining was found in biopsies of minimal change disease, membranous nephropathy, glomerulosclerosis or IgA nephropathy [101].

Urinary and serum MCP-1 levels were evaluated in patients with systemic lupus erythematodes [100, 102] and with various forms of glomerular diseases [103]. In active lupus nephritis urinary MCP-1 levels determined by ELISA were 10- to 20-fold higher in comparison to patients with inactive disease or healthy controls. A high urinary MCP-1 excretion strongly correlated with leukocyte infiltration in the kidneys [100]. In lupus nephritis no correlation was found between urinary MCP-1 levels and proteinuria or serum MCP-1 levels. Treatment of the patients with high doses of glucocorticoids signifcantly lowered urinary MCP-1 excretion and levels decreased to normal values in patients undergoing remission. Rovin, Doe and Tan reported elevated urinary MCP-1 levels in patients with a variety of glomerular diseases [103]. Urinary MCP-1 correlated with the degree of proteinuria, with the number of glomerular macrophages and with the severity of disease. These data support a role or MCP-1 in the macrophage infiltrate of various forms of nephritis.

At present, it appears difficult to reconcile the different immunohistological patterns reported. This may be due to different staining techniques and different sources of antibodies. These discrepancies should be resolved by the exchange of antibodies and tissues between the laboratories and by meticulous attention to details for the handling of samples (such as time from biopsy to tissue fixation). Ideally, expression studies should be complemented by *in situ* hybridization. Finally, different results may reflect the stage of the disease (such as acute vs. chronic, secundary tubular and intersitial ivolvement) and the treatment (such as glucocorticoids) that the patients may have received.

HIV nephropathy

Elevated tissue levels of RANTES, IL-8 and MCP-1 have been reported in biopsies from patients with HIV nephropathy [104]. It is interesting that HIV-associated nephropathy affects predominantly patients of Central African and African American lineage. Most individuals from West and Central Africa are negative for Duffy antigen, that is, they do not express DARC on the surface of their red blood cells. This provides a selective advantage because DARC serves as a receptor for the malarial parasite *P. vivax*. As DARC may function as a clearance mechanism for chemokines, it is speculated that chronic production of the chemokines RANTES, MIP-1α and MIP-1β during HIV infection in the absence of clearance by DARC may result in accumulation of the positively charged chemokines on the negatively charged glomerular filtration barrier, resulting in a perturbation of the

filtration function, leading to proteinuria and potentially to inflammation and mononuclear cell infiltrate. High circulating levels of chemokines could also result in their binding to the second form of DARC present on postcapillary venules of the kidney (as this form of DARC is present in Duffy negative individuals) and thus promote leukocyte "recruitment" to the kidney. At present these are speculations that need to be tested further.

Renal transplant rejection

Levels of RANTES and MIP-1β were found to be increased in kidney transplant rejection using *in situ* hybridization and immunohistochemistry [105, 106]. Both chemokines were found to be expressed by infiltrating mononuclear cells, and by tubular epithelium [105, 106]. In addition, RANTES protein was found on the endothelium of peritubular capillaries, although no local RANTES mRNA production could be detected by *in situ* hybridization. This suggests that RANTES had been bound to the endothelial surfaces, potentially contributing to local T cell and monocyte recruitment [14].

Chemokine expression during renal development

At least one chemokine, RANTES, appears to be expressed in a regulated manner during human renal development [107]. RANTES protein is present in the glomerular mesangium and in the proximal tubules. Interestingly, strong expression of RANTES mRNA was found throughout the developing kidney even in areas that were negative by immunohistology. These results indicate both a developmental and translational control of RANTES expression in these tissues [107]. Although the function of RANTES in kidney development remains to be determined, this finding suggests a role for RANTES distinct from its role as a proinflammatory cytokine [107].

Wilms' tumor and renal cell carcinoma

The production of chemokines by tumor cells or tumor associated cells could explain in part the mononuclear cell infiltrate surrounding these tumors. In biopsy samples Wilms' tumor was found to express the RANTES chemokine [107]. The subcapsular nephrogenic blastema and resident macrophages stained strongly for RANTES protein. By contrast, only one in five renal cell carcinomas was shown to express the RANTES chemokine. However, in each renal cell carcinoma biopsy tested, infiltrating mononuclear cells were found to express RANTES protein [107].

Conclusions, future directions and therapeutic outlook

Renal tissues produce both C-X-C and C-C chemokines *in vivo* and *in vitro* in response to stimulation by agents such as: proinflammatory cytokines, immune complexes, complement activation, and hypoxia. The production of free radicals may represent a common mediator for the activation of chemokines, which also involves transcription factors of immediate early gene responses, among which NF-κB appears to play a central role.

Based on the available data, a hypothetical model for the role of chemokines in acute glomerular and tubulointerstitial injury can be built (Fig. 1). A local insult (immunological, hypoxic, toxic, mechanical, etc.) activates *de novo* chemokine production by, for example: (a) glomerular or peritubular capillary endothelial cells; (b) glomerular or tubular epithelial cells; (c) mesangial or interstitial cells. Other pro- or anti-inflammatory cytokines or mediators may be generated concomitantly. Local activation of platelets may result in release of preformed chemokines (RANTES, MIP-1α, PF4, PBP) and cytokines (such as PDGF) from the platelets directly propagating the inflammatory cascade at the endothelial surface. The chemokines will form a gradient. Once chemokines reach the capillary endothelial surface they will activate circulating leukocytes bearing the respective surface receptors. This will induce interaction of the leukocyte integrin with the adhesion molecules of the immunoglobulin superfamily (such as ICAM-1 and VCAM-1) on endothelial, mesangial and interstitial cells and result in local attachment of the leukocytes. The leukocytes will then transmigrate along the chemokine gradient to the original site of injury and enhance chemokine production at a subendothelial, mesangial, interstitial or epithelial location. The transmigration involves activation of metalloproteinases and plasmin—potentially mediated in part by chemokines—to facilitate diapedesis across basement membranes and extracellular matrix. In this process matrix-bound growth factors, such as TGF-β, and fibroblast growth factors may be activated. These, together with other mediators produced at the original site of tissue injury, will further activate the infiltrating leukocytes. The activation of the leukocytes will initiate their effector functions (such as respiratory burst, phagocytosis of immune complexes, release of hydrolases, removal of matrix, cell debris, and apoptotic cells). Furthermore, the activated leukocytes will produce additional mediators (such as ROS, PAF, leukotrienes, prostaglandins), chemokines, and cytokines (such as IL-1β, TNF-α) that will result in an amplification loop and further leukocyte recruitment. At this point it is possible that infiltrating PMN initially attracted by local IL-8 may now generate monocyte directed chemokines [108] and thus attract monocyte-macrophages. Further along in the inflammatory process, T-cell-specific chemokines might be generated by infiltrating or resident cells and cause a late influx of T-cells which become activated, produce chemokines and factors leading to propagation and amplification of the inflammatory cascade.

A considerable amount of experimental data supports the model up to the point of tissue infiltration. Much less is known, however, about the factors that control the type of chemokine generated and what eventually terminates chemokine and cytokine production and down-regulates the inflammatory response. The latter will determine the eventual outcome of the disease process that is, healing or chronic inflammation resulting in fibrosis.

In this context we would like to raise some questions that need to be adressed in order to better understand chemokine function in renal diseases:

(A) Which factors limit the initial chemokine expression at the site of injury? Is it the short-lasting effect of the stimuli on chemokine mRNA transcription together with the brief half-life of most chemokine mRNAs? Is there down-regulation of chemokine activation upon continued stimulation, and if so, what is the molecular basis?

(B) What determines the pattern of specific chemokines produced at a given time point in the inflammatory process? Many stimuli, such as IL-1, TNF-α, immune complexes or ROS will cause production of a number of chemokines by cultured cells and leukocytes. However, *in vivo* only some chemokines are expressed at a given time point and a restricted repertoire of inflammatory cells is recruited. Furthermore, *in vivo* chemokine expression seems to follow a certain time course, that is, different chemokines

may be generated sequentially. Does this involve a cell-type specific temporal pattern of chemokine expression? Could chemokine generation be more restricted *in vivo* because of cell-cell or cell-matrix interactions or because of a specific local milieu that is a composition of various stimulatory and inhibitory mediators? Another factor that could influence the specifity of the cell infiltrate could be the expression pattern for the chemokine receptors on the leukocytes, which might also be influenced by inflammatory mediators.

Some of these questions may also be relvant for the interaction of infiltrating inflammatory cells with the local resident cells. For example, could the engagement of leukocyte integrins with ICAM-1 or VCAM-1 on the resident cells terminate or amplify the chemokine production or alter its pattern from a previously PMN-specific one to one directed towards monocytes or T cells?

(C) Do chemokines fulfill different functions as the inflammatory process progresses? For example, can a massive local chemokine production as it may occur at the site of an inflammatory infiltrate with its amplification loops, eventually result in a downregulation of the response of the target leukocytes, similar to what is observed with systemic administration of chemokines? Can high concentrations of chemokines, perhaps in combination with other local mediators, influence apoptosis?

(D) What is the role of chemokines in repair processes, in chronic inflammatory processes and in fibrosis? For example, chemokines may influence metalloproteinases and some C-X-C chemokines appear to have angiogenic and antifibrogenic capabilities.

These are intriguing questions that need to be addressed in order to clarify our picture of the role of chemokines in renal diseases. Answers to these questions will require a multipronged approach including studies on signal transduction and gene regulation at the molecular level in cultured cells. Potentially new functions of chemokines (such as angiogenesis and cell survival) can initially be investigated *in vitro* and then have to be verified *in vivo*. Additional detailed time course studies and investigations on the cellular sources for chemokines have to be performed in experimental models of renal diseases using immunohistology and *in situ* hybridization. The question of which specific chemokine is produced in response to a defined injury should also be clarified by these experiments. Furthermore, interference with chemokine generation and function needs to be attempted. The contribution, if any, of chemokines to chronic fibrosing processes should be evaluated by a comparable approach. Generation of chemokine and chemokine receptor knockout mice may provide hints for new chemokine functions. Finally, complementary evaluation of human kidney biopsy material must validate the experimental findings.

Since multiple roles for chemokines at various stages of inflammatory processes have been described (Fig. 1), one can envision many levels at which to interrupt the various actions of the chemokines to affect inflammation [41, 109]. For example, the expression of chemokines by fibroblasts, endothelial and epithelial cells induced by proinflammatory cytokines may be suppressed by soluble TNF receptor or IL-1 receptor antagonists [110]. Glucocorticoids inhibit transcription of several chemokine genes including IL-8 [111], MCP-1 [112] and RANTES [113]. Agents that interfere with matrix and surface binding of chemokines such as heparin may influence chemokine effects [114]. Humanized neutralizing antibodies or competitive inhibitors directed against chemokines and/or their receptors may be effective [115, 116]. Finally, it may be possible to develop selective inhibitors of the signal transduction pathways downstream of the chemokine receptors. Given the apparent redundancy of function described for many of these molecules, it is unclear whether the suppression of a single chemokine will be therapeutically useful. It is also unclear whether such agents will have deleterious side effects such as nonspecific immunosuppression. Nonetheless, influencing chemokine generation and action may turn out to be of considerable therapeutic benefit.

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Note added in proof

After submission of the manuscript several important papers have been published. A new human chemokine receptor (CXCR-3) specific for IP-10 and Mig was identified [117]. The lymphocyte chemoattractant SDF-1 has been shown to act as a ligand for the chemokine receptor CXCR-4 (LESTR/fusin). This receptor can function as an entry cofactor for T cell line-tropic isolates of HIV-1 [118, 119, 120]. A deletion has been found in the CCR-5 gene which appears to confer resistance to HIV-1 infection in homozygous individuals [121, 122].

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